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CASE REPORT

Therapy-Related Acute Lymphoblastic Leukemia with Plasmablastic Morphology after Myeloma: a Pitfall

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ABSTRACT

Background: **Therapy-related acute lymphoblastic leukemia (t-ALL) after multiple myeloma (MM) treatment is a rare complication linked to lenalidomide and autologous stem cell transplantation (ASCT). Diagnosing t-ALL vs. MM relapse is challenging when blasts show plasmablastic morphology.**
Methods: **An elderly male with IgA-λ MM, previously treated with double ASCT and lenalidomide, presented with fatigue and hematochezia. Pancytopenia was noted. Bone marrow showed 35.0% plasmablastic cells, raising concern for relapse.**
Results: **Flow cytometry confirmed CD34/TdT/CD19-positive B-ALL, not myeloma. Karyotype was normal; NGS revealed a DNMT3A mutation, typical of therapy-related leukemia. This supported t-B-ALL diagnosis.**
Conclusions: **This case highlights a diagnostic pitfall where morphology misleads. Integrated lab analysis - especially flow cytometry - is essential to classify complex malignancies and guide therapy, underscoring therapy-related leukemogenesis in MM survivors.**
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KEYWORDS

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INTRODUCTION

Multiple myeloma (MM) is a hematologic malignancy characterized by the clonal proliferation of plasma cells in the bone marrow. The therapeutic landscape for MM has been revolutionized by novel agents like proteasome inhibitors and immunomodulatory drugs (IMiDs), alongside autologous stem cell transplantation (ASCT), significantly improving patient survival. However, this success has been shadowed by the increased recognition of long-term complications, particularly therapy-related secondary neoplasms [1].
Therapy-related myeloid neoplasms (t-MNs), including acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS), are well-documented sequelae. In

stark contrast, therapy-related acute lymphoblastic leukemia (t-ALL) is rare but carries a grave prognosis [2, 3]. Its diagnosis is profoundly challenging. When a patient with a history of MM presents with cytopenias and a marrow infiltrated by immature cells, the initial suspicion is always disease relapse. This challenge is compounded when the leukemic blasts exhibit plasmablastic morphology, closely mimicking the appearance of immature plasma cells, leading to a critical diagnostic pit fall [4].

This case report describes a patient with MM who developed t-ALL with plasmablastic morphology after double ASCT and lenalidomide maintenance. We highlight the indispensable role of an integrated diagnostic approach, led by multiparameter flow cytometry, in resolving this dilemma and guiding appropriate clinical management.

CASE PRESENTATION

An elderly male patient was initially diagnosed with IgA-λ type multiple myeloma in May 2018 following an anemia workup during a routine health examination. Comprehensive evaluation at Tianjin Hematonosis Hospital confirmed the diagnosis, classifying his disease as Durie-Salmon stage IIIA, International Staging System (ISS) stage III, with 1q21 amplification. His treatment course began with induction therapy consisting of four cycles of VRD chemotherapy (bortezomib, lenalidomide, dexamethasone) administered between May and November 2018. He subsequently underwent his first autologous hematopoietic stem cell transplantation (ASCT) in December 2018. Following successful transplantation, he received one consolidative cycle of VRD and initiated maintenance therapy with lenalidomide. Unfortunately, the patient self-discontinued maintenance therapy at an unspecified timepoint. In December 2021, routine surveillance revealed disease relapse with bone marrow examination showing 22.5% plasma cells. He received two cycles of VRD re-induction therapy (December 2021 and January 2022) followed by a second ASCT in March 2022. Post-transplant evaluation in October 2022 confirmed complete response, and he resumed lenalidomide maintenance therapy.

The patient presented to our institution in March 2025 with a one-week history of progressive fatigue, hematochezia, and increased nocturia. Initial evaluation at a local hospital revealed pancytopenia, prompting referral to our center for specialized management. Physical examination on admission revealed a frail-appearing but alert elderly male. Vital signs were stable with normal cardiopulmonary examination. Abdominal examination was unremarkable without hepatosplenomegaly or tenderness. No peripheral edema was noted. Admission laboratory studies confirmed significant pancytopenia: leukopenia (WBC 1.25 x 10^9/L), neutropenia (ANC 0.51 x 10^9/L), anemia (Hb 119 g/L), and thrombocytopenia (PLT 97 x 10^9/L). Hepatic function panel showed mild transaminitis and hyperbilirubinemia. Chest CT demonstrated a small residual pulmonary infiltrate improved from previous studies. Initial management focused on supportive care with granulocyte colony-stimulating factor for neutropenia and hepatoprotective therapy for drug-induced liver injury. Given the persistent cytopenias despite supportive measures, a bone marrow biopsy was performed to evaluate for disease relapse versus other hematologic complications. The critical diagnostic breakthrough came from integrated bone marrow analysis. Morphological assessment demonstrated a hypercellular marrow with 35.0% immature cells showing plasmablastic features (Figure 1), initially suggestive of aggressive myeloma relapse. However, multiparameter flow cytometry revealed a distinct immunophenotypic profile positive for CD34, TdT, CD19, and CD10 (Figure 2), unequivocally establishing the diagnosis of common B-cell acute lymphoblastic leukemia (high-risk group). The recommended frontline therapy with Blincyto combined with intensive chemotherapy was proposed. However, the patient declined this approach. Consequently, alternative induction therapy with the mini-HyperCVD-V regimen was initiated on April 18, 2025, consisting of VCR 2 mg on days 1 and 8; Dex 20 mg on days 1 - 4 and 11 - 14; CTX 200 mg q12hour on days 1 - 2 and 300 mg q12hour on day 3; and Venetoclax with dose escalation (100 mg on day 6, 200 mg on day 7, and 400 mg on days 8 - 14). Post-treatment assessment revealed minimal residual disease (MRD) for B-ALL at 0.027%, while serum M-protein remained undetectable. Despite recommendations for continued systemic chemotherapy, the patient ultimately refused further treatment and requested discharge.

This case illustrates the diagnostic challenge of distinguishing between myeloma relapse and therapy-related secondary leukemia, emphasizing the crucial role of multiparameter flow cytometry in establishing accurate diagnosis.

DISCUSSION

This case exemplifies a profound diagnostic challenge in modern hematology. The patient's history and the plasmablastic morphology of the malignant cells strongly pointed towards a relapse of his multiple myeloma. However, comprehensive immunophenotyping by flow cytometry was unequivocal, revealing a B-ALL immunophenotype (CD34+/TdT+). This critical finding reclassified the disease and entirely altered the therapeutic pathway, underscoring that morphology, while essential, can be misleading and must be corroborated by immunophenotyping in such complex scenarios [4].

The development of t-ALL is a rare but devastating late effect of MM therapy. Our patient had several key risk factors: exposure to an alkylating agent (melphalan for ASCT) and prolonged lenalidomide maintenance therapy, both of which have been implicated in the pathogenesis of therapy-related leukemias [2,5]. The presence

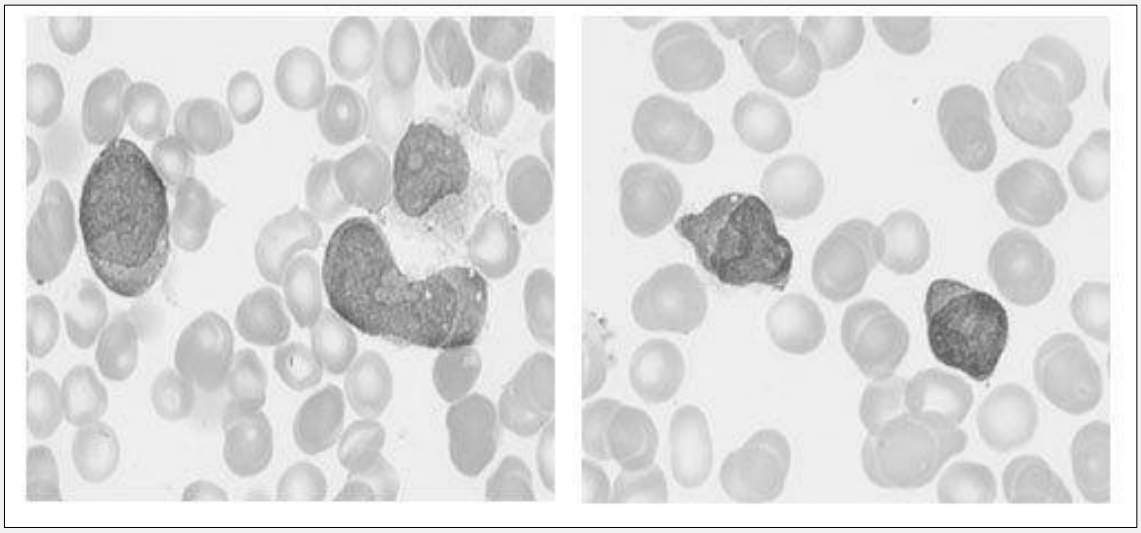

Figure 1. Bone marrow aspirate with plasmablastic features.

Hypercellular marrow showing 35.0% immature cells exhibiting eccentric nuclei, prominent nucleoli, and basophilic cytoplasm (Wright-Giemsa stain, 1,000 x). Findings were suspicious for myeloma relapse.

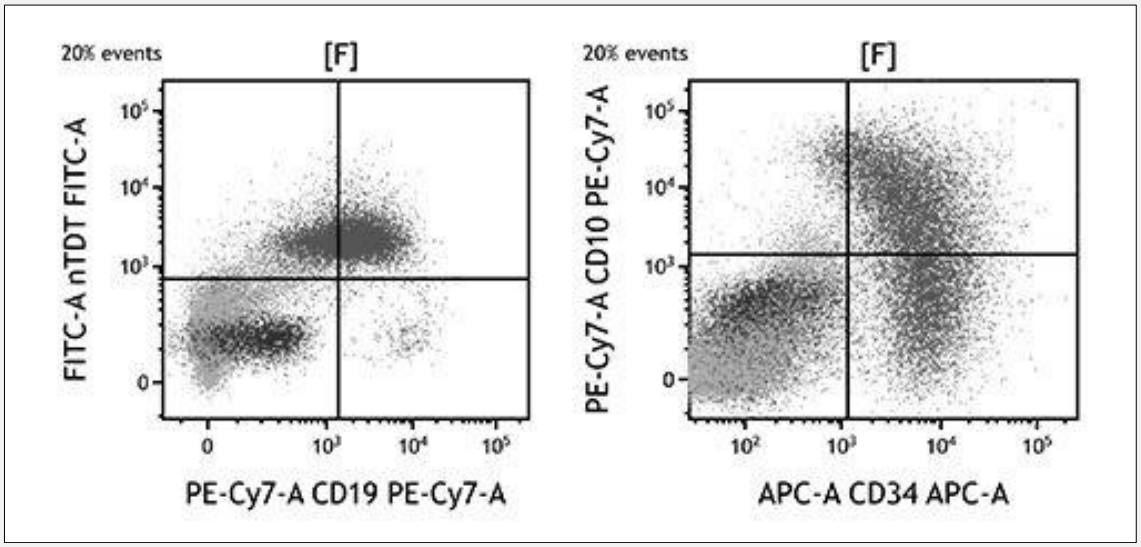

Figure 2. Multiparameter flow cytometric analysis of bone marrow aspirate.

The analysis revealed a distinct population of blasts positive for CD34, TdT, CD19, and CD10, consistent with a diagnosis of common B-cell acute lymphoblastic leukemia (B-ALL) and excluding a plasma cell neoplasm.

of a DNMT3A mutation, while uncommon in de novo ALL, is a frequent finding in therapy-related myeloid and lymphoid neoplasms, further supporting the iatrogenic origin of this leukemia [6].

The prognosis for patients with t-ALL is generally poor, and treatment represents a formidable dilemma. These patients often have reduced bone marrow reserve from prior therapies and are of advanced age, making them poor candidates for intensive chemotherapy. Allogeneic stem cell transplantation may offer the only chance for cure but is associated with high treatment-related mortality [3,7]. Our patient's refusal of treatment reflects the difficult choices and grim outlook faced in this situation.

This case adds to the small but growing body of literature on t-ALL post-MM therapy [2,8,9]. It serves as a critical reminder for clinicians and pathologists to maintain a high index of suspicion for secondary malignancies in MM survivors presenting with new cytopenias or atypical marrow findings and to routinely employ flow cytometric analysis to avoid misdiagnosis.

CONCLUSION

We present a classic case illustrating a significant diagnostic pitfall in which therapy-related B-acute lymphoblastic leukemia (t-B-ALL) mimicked myeloma relapse due to its plasmablastic morphology. This case highlights several critical lessons: first, the diagnosis of relapse in multiple myeloma is not always straightforward, necessitating a high index of suspicion for secondary neoplasms; second, flow cytometry is an indispensable and non-negotiable tool in the diagnostic workup of ambiguous hematologic malignancies, providing essential clarity beyond morphological assessment; third, the therapeutic success achieved in multiple myeloma carries a long-term cost, underscoring the necessity of vigilant, long-term monitoring for therapy-related complications as a core component of survivorship care; and ultimately, an integrated, multimodal diagnostic approach is paramount to ensure accurate diagnosis and guide appropriate management in such complex clinical scenarios.

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Ethics Approval:
Informed consent was obtained. The study complied with the Declaration of Helsinki.

Data Availability:
Original data available upon request.

Declaration of Interest:
The authors declare no competing interests.

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